

The Harrell Study and Seven Follow-Up Studies: A Brief Review¹

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In 1981, R.F. Harrell and coworkers reported substantial IQ gains and other benefits in a partially double-blind, exploratory study of nutritional supplements and thyroid given to mentally retarded children (Harrell, Capp, Davis, Peerless & Ravitz, 1981). These findings attracted wide interest, controversy, and seven follow-up studies to date. The purpose of this review is to present a brief overview of these eight studies and to evaluate the scientific status of the issues raised by the Harrell study.

In the original study, sixteen school-age children living at home (IQ 17-70) received dietary advice and nutritional supplements or placebos during a planned 8-month study. Desiccated thyroid was also given throughout to 13 of the subjects, as required to maintain morning axillary temperature at 36.6° C or above (Barnes method). The supplement contained 11 vitamins, most in large amounts, and 8 minerals in moderate amounts. During the first 4-month period (double blind), the 5 children receiving supplements (and thyroid) recorded average IQ gains of 5 to 10 points, depending on the investigator. However, the 11 placebo (and thyroid) subjects showed negligible average change (1 point), indicating that thyroid alone did not increase IQ in this experiment. In the second 4-month period, both groups received supplements plus thyroid. The IQs of the prior placebo subjects increased a reported 10 points on average, especially in the younger subjects, while some of the previously supplemented

group showed additional gains. Three of four Down syndrome subjects recorded IQ gains of 11 to 24 points and showed physical changes toward normal. Other behavioral and health benefits also were reported.

Disappointingly, seven later studies using nearly the same nutritional supplement with about 125 retarded children and adults have all reported no significant average IQ gains (see Table). Furthermore, with the exception of one 18-point gain in a placebo subject, the later studies all reported no individual gains exceeding 10 points, whereas Harrell jointly with her co-testers reported gains of over 10 points in many subjects (5 of 16 after 4 months and about 9 of 16 after 8 months of supplementation). Also, seemingly none of the later studies have confirmed the academic, behavioral, or physical improvements noted by Harrell et al. However, it is difficult to evaluate conclusions without data, such as, "no consistently striking reports of observed improvements" (Smith, et al., 1984).

The discrepancies between the results of Harrell and the seven later studies seem clear-cut, and they beg for exploration. Four of the follow-up studies involved institutionalized adults much older than Harrell's subjects (see Table; groups led by Ellis, Coburn, Ellman and Chanowitz). As noted by some of these researchers, the age and low IQ of their subjects and the subjects' relative lack of stimulation from school and home all made them unpromising candidates for quick improvements. Although worthwhile, these four experiments do not assess the reproducibility of Harrell's findings in home-living children.

The remaining three studies more nearly approached the age of IQ of Harrell's subjects (see Table; Weathers, Bennett, and Smith groups). All three used entirely Down syndrome subjects who were more

1. Based on part of a chapter by D.R. Davis, "Nutritional Therapy in the Prevention and Reversal of Mental Retardation," in: *Preventive and Curative Interventions in Mental Retardation*, by F.J. Menolascino & J.A. Stark, editors, Baltimore: Brooks Pub. Co., 1987.

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Author* & Date	Subjects (No.)	Male (%)	Mean Age & Range	Mean IQ & Range	Home Living
Harrell 1981	16 4 Down	38	9.5 5-15	48 17-70	yes
Ellis 1983	40 10 Down	60	29 21-40	26 12-40	no
Weathers 1983	47 All Down	66	11.4£ 6-17	46 30-67	yes
Bennett 1983	20 All Down	50	10.5 5-13	49 26-76	yes
Coburn 1983	38 9 Down	74	24 16-30	29 10-49	no
Ellman 1984	20 4 Down	50	22 16-24	39 22-56	no
Smith 1984	56 All Down	71	11.2 7-15	46 28-76	yes
Chanowitz 1985	37 ?	?	26 ?	15? ?	no

* Harrell, Capp, Davis, Peerless & Ravitz, 1981

Ellis & Tomporowski, 1983

Weathers, 1983

Bennett, McClelland, Kriegsmann, Andrus & Sells, 1983

§ S = supplement, P = placebo, T = thyroid gland or hormone

S modifications: no biotin — Harrell; 1/3 vit. A after 4 mo. — Smith

MA = mental age

£ Weathers, J.C., Ph.D. dissertation, Georgia State Univ., 1982

¶ Said to approximate 1.5 grains/day desiccated thyroid

predominantly male than Harrell's subjects, but these two differences seem unable to explain the discrepant results, because Harrell's Down syndrome and male subjects did as well as the others. The major experimental difference in these three studies (which also applies to the adult studies except perhaps one which used 1-thyroxine) is their omission of the desiccated thyroid given to 13 of 15 subjects who needed it according to the Harrell protocol. This omission and possible synergistic interactions between thyroid and nutrients may be the only remaining hope that Harrell's findings can yet be reproduced in unselected groups.

The "thyroid explanation" receives perhaps slight support from a 7-point IQ gain in one subject coincidentally taking

1-thyroxine in the study by Ellman, et al. (1984) and from a recent anecdotal report (Rimland & Davis, 1986). However, it is weakened by average 13-point IQ gains in the two Harrell subjects who didn't take recommended thyroid. An important experiment in progress led by Menolascino includes desiccated thyroid (although in uniform dose) and will provide the first near replication of Harrell's study. (Some of the later researchers described their work too loosely as attempted "replications"; some failed to mention their omission of thyroid, and one downplayed the omission by misrepresenting Harrell's use of thyroid as "intermittent.")

Thyroid was omitted in the later studies mainly because of objections to the unorthodox method of prescribing it in the Harrell

Thyroid Used	Design§	Group	IQ: Chng: Mean (Range)		IQ Tests	
			4 Months	8 Months		
Desiccated Barnes meth. 0.5-2 gr./day	ST1	ST1 5 (-2/10)	14(6/22)	S. Binet 84%	WISC-R 10% Cattell 6% S. Binet S. Binet S. Binet S. Binet Leiter95 % S. Binet 5% WISK-R 50% WPPSI 50% Cattell 57% S. Binet 43%	
	PT ST2 (ST2)	ST2 PT	10(2/22) 1 (-7/5)	16(2/24)		
	no	S(7mo.) P (7 mo.)	S P	-		-1(11 4) -1
	no	S P	s p	1 (-9/7) £ 3 (-5/18)		—
	no	S P	s p	—		-1 (-6/9) 1 (-7/6)
	no	S (20 week) P (20 week)	s p	0 0		—
no	S (6 mo.) P(6mo.)	s p	1 (-4/7) 1 (-9/8)	-		
no	SS PP	s p	0 0	-1 (-9/9) -1 (-8/?)		
1-thyroxin 0.15 mg/day	ST SP PT PP	ST SP PT PP	1 mo. MAS Omo. MA Omo. MA Omo. MA	-		

Coburn, Schaltenbrand, Mahuren, Clausman, & Townsend, 1983; Ellman, Silverstein, Zingarelli, Schafer, & Silverstein, 1984; Smith, Spiker, Peterson, Cicchetti, & Justine, 1984; Chanowitz, Ellman, Silverstein, Zingarelli & Ganger, 1985

study. The Barnes functional method calls for giving thyroid to many individuals who do not need it according to current methods based on serum levels of thyroid hormones. Also, Harrell's thyroid-plus-placebo group showed no significant IQ change, and this fact regrettably led one research group to the unwarranted conclusion that "therefore, thyroid medication did not influence (Harrell's) final results" in the thyroid-plus-supplement group (Davis & Capp, 1985).

Other explanations for the discordant findings have been suggested or implied. The Harrell study was not fully double blind after the first 4 months, and strong investigator expectations may have affected half of the IQ tests at 8 months as well as other outcomes reported. Significantly, however, blind and sceptical independent testers reported IQ gains of 11 to 16 points in 4 or 5 of 15 subjects (S.R., T.C., D.D., S.O., R.S., who all took thyroid). This many large individual gains contrasts sharply with the tiny incidence of gains over 10 points in the studies led by Weathers, Bennett, and Smith (1 out of 123; $P < 0.0005$ by Fisher's exact test).

The several large individual gains in Harrell's report are also inconsistent with the implication of Smith, et al. (1984) that their superior matching of supplement and placebo groups and control of other variables could explain the discrepant findings (Davis & Capp, 1985). No amount of matching or variable control with Harrell's subjects could change their large IQ gains which are the crucial and so far unexplained difference between the results of the Harrell group and others.

Instead, attention should focus first on whether the several 11- to 24-point IQ gains recorded for the Harrell subjects were accurate. If Harrell and the licensed and certified independent testers were all incorrect about these large gains, there may be no conflict with the three subsequent studies in children, and no need for further explanation. On the other hand, if the independently verified gains were accurate, the problem becomes one of discovering why they occurred

and whether they can be reproduced. If the gains were accurate and were facilitated by factors such as thyroid or investigator belief and enthusiasm, then the Harrell study is an important discovery (or rediscovery) with broad implications requiring further elucidation.

If Harrell's reported gains were accurate but cannot be reproduced by true replications in other groups of retarded children, then the Harrell study probably has little significance beyond her subjects. For example, Harrell's subjects from Norfolk, Virginia might represent a selected population of unusual retarded children with nutrient-responsive metabolic defects or heavy metal toxicity (Davis, 1987). Over 1,000 individually rare inborn errors of metabolism are known to cause mental retardation, and some of these defects respond to nutritional supplementation (Davis, 1987). Although it may be unlikely, the possibility of differing populations cannot presently be excluded, because many of the Harrell group's subjects had hearing and visual problems, motor handicaps, or disorders such as epilepsy which apparently would have excluded them from at least most of the later studies.

The cited experiment in progress which includes thyroid should narrow the possible interpretations of the eight studies reviewed. If this remaining hope proves vain, then further evaluation of the study by Harrell, et al. will depend on whether the reported large IQ gains are judged credible, and if so, whether the evidently unusual conditions required to produce the gains can be determined.

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Vitamins and Minerals in Down Syndrome

The following interchange appeared in the Journal of Pediatrics, March 1985, Vol. 106, No. 3, p. 531.

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To the Editor:

Smith et al.¹ give worthwhile data in their follow-up to the study of Harrell et al.² However, a key premise and conclusion are incorrect, and parts of the discussion are inadequate and misleading.

Smith et al. tested nearly the same supplement as did Harrell, but like all others to date, did not test it under Harrell's conditions, in which desiccated thyroid was given simultaneously. Hence there have been no true replications of the Harrell regimen. Although at least some investigators recognize this important fact, Smith et al. ignore possible synergistic interactions of thyroid and nutrients and state as fact their unwarranted *speculation* that "thyroid medication did not influence (Harrell's) final results." The only proper basis for such conclusion would be a protocol (never used) giving the supplement with and without thyroid. We regret that Smith et al. ignored our repeatedly bringing these points to their attention long before publication and also misleadingly failed to mention their omission of thyroid in a preliminary report.³

Smith et al. defend their speculation that thyroid did not affect Harrell's results (and would not have affected their own) on the basis that their subjects did not need thyroid according to standards tests and on the basis of their claim that Harrell's subjects received thyroid only "intermittently." As has been emphasized to Smith, Harrell's subjects received thyroid *continuously*, adjusted in amount based on axillary temperatures measured periodically, a method well known to often call for thyroid when other tests do not.

Other misleading claims include their incorrect implication that their superior subject matching or control of other variables could explain the difference between their findings and those of Harrell. Fortunately, a more exact replication of the Harrell regimen is under way.

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2. Harrell RF, Capp RH, Davis, DR, Peerless J, Ravitz LR: Can nutritional supplements help mentally retarded children? An exploratory study. *Proc Natl Acad Sci USA* 78:574, 1981.
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Reply

To the Editor:

The arguments put forth by Drs. Davis and Capp are well known to me, and I only wish their conclusions were correct. Unfortunately, there are no scientific publications supporting their position. In addition to our publication¹ there are now two others^{2,3} that support our findings. Contrary to Dr. Davis's impression, I would love to see scientific data that would show that this type of treatment is beneficial to children with Down syndrome. It is now up to Dr. Davis to supply us with these scientific data.

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